Potential for Environmental and Therapeutic Agents to Induce Immunotoxicity

NTP Board of Scientific Counselors
Concept Review

October 26, 2004

NIEHS
The National Institute of Environmental Health Sciences
The National Institutes of Health
The Department of Health and Human Services

NTP
The National Toxicology Program
The Department of Health and Human Services

Purpose of the Contract

- Develop and validate methods to evaluate modulation of immune function
- Evaluate immunomodulatory potential of agents of concern using a tiered testing panel
- Studies to define cellular and molecular events associated with modulation of immune function

Historical Information

- Testing contract has been available since the 1980.
  - Proposals sought in 1985, 1990, 1995 and 2000
  - Current contractor is Virginia Commonwealth University
- Separate ITOX contracts for specific agents
- In house studies

Historical Information

- Current Contract
  - Five year contract with R &D and additional task options
- Proposed Contract
  - Three year base contract with five additional years, R & D and additional task options

Impact of NTP ITOX efforts

- Developed tiered testing panel which has been the basis for regulatory guidelines and guidance in the field
- Provided leadership in evaluating predictive methods
- Risk assessment and extrapolation to human health

Source of Nominations

- NTP Chemicals of Interest
- Other Agencies
- ICCEC
- Academic Community
- General Public

Current Annual Activities

- Immunomodulation
  - Generally in B6C3F1 mice and/or F344 rats
  - Exposure can be oral, i.p., dermal, dosed food or water
  - Inhalation exposures can be done as add on
  - 4 Range finding studies and 2 Protocol studies
- Hypersensitivity
  - Balb/c mice
  - 2 Compounds
- Autoimmunity
  - 1 Compound

Range Finding Studies to Screen for Immunomodulatory Effects

- Immunopathology
- Cell Mediated Immunity
- Humoral Mediated Immunity
- Non-Specific Immunity
- Cell Quantification

Chemicals Tested in Range Finding Studies

- Saquinavir
- Itraconazole
- AZT
- Nevirapine
- Echinacea purpurea
  - NTP Preparation
  - Commercial Prep
- Chloroform
- Chloramine
- Dibromoacetic Acid
- Dichloroacetic Acid
- Phenol
- 1,3-Dichloropropene

Chemicals Tested in Range Finding Studies (continued)

- Ethinyl Estradiol
- Vinclozolin
- Elmiron
- Patulin (Rat)
- Patulin (Mouse)
- Hexavalent Chromium (mouse)
- Hexavalent Chromium (rat x 2)

Full Protocol Studies to Evaluate Immunomodulatory Effects

- Immunopathology, Humoral Mediated Immunity and Cell Quantification from Range finding studies plus additional tests to assess:
- Cell Mediated Immunity
- Humoral Mediated Immunity
- Non-Specific Immunity
- Hematopoietic Stem Cells
- Host Resistance

Chemicals Tested in Protocol Studies

- Saquinavir
- Dibromoacetic Acid
- Chloroform
- Echinacea purpurea
- Elmiron

Assessment of the Potential to Induce Hypersensitivity

- Local Lymph Node Assay
  - ICCVAM protocol
  - Modification to evaluate systemic hypersensitivity
- Mouse Ear Swelling Test
- Cell Quantification in LN
- Cytokine mRNAs

Chemicals Tested for Potential to Induce Hypersensitivity

- 5- Amino-*o*-Cresol
- Pyrogallol
- Rifamycin
- Sodium Metasillicate
- Annatto
- Norbixin

Potential to Influence Autoimmune Disease

- Models
  - NZB Mouse (Systemic Lupus erythematosus)
  - NOD mouse (Diabetes)
  - Brown Norway Rat (Autoimmune skin and renal disease, SLE)
- Endpoints
  - Quantification of autoantibodies, serum Ig levels, protein and glucose in urine, histology

Chemicals Evaluated for Potential to Induce or Exacerbate Autoimmune Responses

- Cadmium
  - NZB Mouse
  - Brown Norway Rat
  - Mrl/lpr mouse
- Genistein
  - NZB Mouse
- Echinacea
  - NZB mouse

R & D Developmental Studies

- Tributyltin Oxide
- AZT
- Nevirapine
- Vinclozolin
- Ethinyl Estradiol
- CpG Oligonucleotide

R&D Studies

- Transgenic Mouse studies
- Immunotoxicogenomics studies
- *In vitro* methods
- Keyhole Limpet Hemocyanin as an alternative antigen
- ELISPOT technology
- Improving Delayed Type Hypersensitivity models
- Improving Host Resistance models
- Electronic Database

Products

- Over 25 publications in peer-reviewed journals
- Mechanistic studies
  - Tissues from testing efforts used to conduct hypothesis driven research
- NTP Reports

New Features for 2005

- Routine evaluation of tissues using extended histopathology
  - Additional data needed for evaluation of sensitivity and specificity

New Features for 2005

- Routine collection of tissues for genomics studies
  - Correlation between altered function and changes in gene expression
  - Focused versus tissue-specific arrays
  - Can gene fingerprinting be used to screen for compounds that target the Immune system?

New Features for 2005

- Inclusion of developmental studies as a defined task
  - Evaluation of test methods
  - Identification of new endpoints to assess the developing immune system
  - Persistence of effects in adult animals

Annual Activities

- Immunomodulation
  - 4 Range finding studies
  - 2 Protocol studies
  - 2 Developmental Studies
- Hypersensitivity
  - 2 Compounds
- Autoimmunity
  - 1 Compound

Options

- Test Additional Compounds
  - May be exercised in any year of the contract
  - Can increase capabilities by 35% of the total yearly level of effort
- Mechanistic Studies and Development of New Technology
  - May be exercised in any year of the contract
  - NTE 10% of base contract

Summary

- Statement of work similar to previous contracts
  - Routine inclusion of additional endpoints
  - Capacity can be increased through use of Task V options
- Addition of task for evaluation of developmental immunotoxicity
- Shorter base contract with additional years as options

Looking forward

- Develop and validate methods to evaluate modulation of immune function
  - Use of in vitro and genomics studies for screening
- Evaluate immunomodulatory potential of agents of concern
  - Focus on susceptible populations (neonates, aged animals) and specific diseases (autoimmunity)
- Studies to define cellular and molecular events associated with modulation of immune function
  - Not just yes and no, but why and how